Conferences and Reviews

Orthostatic Hypotension
Causes, Evaluation, and Management

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Chronic orthostatic hypotension is caused by a variety of disorders. Frequently patients withdraw from social interactions, are prone to adverse drug reactions and inappropriate diagnoses, and are bed-bound by the time of diagnosis. Applying basic principles of cardiovascular physiology and pharmacology usually permits these patients to lead active lives and to live longer. Much of the management is based on common sense and knowledge of the basic pathophysiology of the disorder and depends on thorough patient education and close monitoring of blood pressure in many of the activities of daily living.

(Hollister AS: Orthostatic hypotension—Causes, evaluation, and management. West J Med 1992 Dec; 157:652-657)

Orthostatic hypotension may be defined as any postural fall in blood pressure that results in symptoms referable to cerebral hypoperfusion. This definition purposefully avoids absolute values for blood pressure because a wide range of cerebral perfusion pressures may be tolerated by individual patients. The prevalence of chronic orthostatic hypotension in the general population has been estimated at 5 per 1,000,[1] but the incidence of orthostasis in acute medical care settings ranges from 7% to 17% of all patient contacts.[2,3]

Causes of Orthostatic Hypotension

A wide variety of medical conditions may primarily or secondarily cause orthostatic hypotension. These may be broadly categorized as reduced effective blood volume, drug-induced hypotension, miscellaneous disorders, and autonomic disorders.[1,4-6]

Reduced effective blood volume may result from various conditions. Acute and subacute intravascular volume losses due to hemorrhage, burns, sepsis, dialysis, excessive diuresis or sweating, hyperglycemia, and diabetes insipidus are readily apparent causes of orthostasis, accompanied by pronounced tachycardia. Intravascular volume contraction occurs frequently in pheochromocytoma, Addison's disease, vipomas, chronic diarrheal illnesses (especially cholera), renovascular hypertension, salt-losing nephropathy, and anorexia nervosa. A relative insufficiency of intravascular volume is present in large venous varicosities, left-to-right shunts, arteriovenous malformations, absence of venous valves, the last trimester of pregnancy, hyperthyroidism, beriberi, and probably mitral valve prolapse. Paroxysmal hypovolemia may be caused by the dumping syndrome, hyperosmolar feedings (particularly following gastrectomy), hypermagnesemia, and the release of excessive amounts of vasodilators in carcinoid syndrome, mastocytosis, and hyperbradykininism.

The drugs most commonly causing symptomatic orthostatic hypotension are listed in Table 1. Miscellaneous causes of orthostatic hypotension include cardiac dysrhythmias, angina, heart failure, pulmonary embolism, atrial myxoma, hypokalemia, paraneoplastic syndromes, and the sympathetic deconditioning that occurs with prolonged bed rest or weightlessness.

Autonomic Disorders Causing Orthostatic Hypotension

The major neurogenic causes of orthostatic hypotension are the Shy-Drager syndrome,[7] idiopathic orthostatic hypotension,[8] peripheral neuropathies, and parasympathetic reflex activation. Lesions and surgical procedures in the posterior fossa and upper cervical spinal cord may interrupt the autonomic control of blood pressure or heart rate or both, resulting in orthostatic hypotension. Other causes may include hydrocephalus, medullary plate syndromes, Wernicke's encephalopathy, multiple cerebral infarcts, multiple sclerosis, craniopharyngioma, and syringomyelia. Major neurologic defects associated with orthostatic hypotension—the Shy-Drager syndrome or multiple system atrophy—include Parkinson's disease, pseudobulbar palsy, cerebellar degeneration, and olivopontocerebellar atrophy. Familial dysautonomia—the Riley-Day syndrome—is an inherited disorder with widespread neurologic deficits and autonomic dysfunction.[9] Recently, encephalopathy due to the acquired immunodeficiency syndrome has been associated with orthostatic hypotension and multiple neurologic deficits.[10,11] Each of these central nervous system causes of orthostatic hypotension may be viewed as a disconnection of the central

TABLE 1.—*Drugs Causing Orthostatic Hypotension*

Tricyclic antidepressants	Alcohol
Sympatholytics	Narcotic agents
Vasodilators	Vincristine sulfate
Diuretics	Perhexiline
Phenothiazine derivatives	Sympathomimetic agents (prolonged use)
Minor tranquilizers	Marijuana
Nitrates	
Insulin	

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integrative control of blood pressure from the peripheral autonomic nervous system.

Idiopathic orthostatic hypotension—the Bradbury-Eggleston syndrome—is caused by a progressive loss of the peripheral preganglionic and postganglionic autonomic nerves for reasons that have not yet been elucidated. Sympathicotonia, a poorly defined and poorly understood syndrome associated with orthostatic tachycardia, malaise, and psychiatric disturbances, also has been called neurasthenia, the effort syndrome, soldier's heart, somasthenia, DaCosta's syndrome, neurocirculatory asthenia, and hyperadrenergic syndrome.[12-15] From the 1940s through the early 1960s, lumbar sympathectomies were occasionally used to treat uncontrollable hypertension and resulted in marked orthostatic hypotension.[16] Baroreceptor dysfunction caused by irradiation, surgical treatment, tumor, or glossopharyngeal neuralgia may result in paroxysmal orthostatic hypotension, a blood pressure that is directly dependent on the heart rate, or both.[17] The activation of parasympathetic reflexes—with and without sympathetic withdrawal—by hollow viscus distension, increased intraocular pressure, carotid sinus pressure, swallow, hiccup and cough, vasovagal reactions (including the Bezold-Jarisch reflex), myocardial ischemia, and micturition all result in paroxysmal falls in blood pressure.[6,18] Dopamine-β-hydroxylase deficiency has been described as a cause of profound orthostatic hypotension coupled with an absence of norepinephrine synthesis.[19]

Many forms of peripheral sensory and motor neuropathy may also involve the autonomic nervous system and result in orthostasis (Table 2). Of the causes listed, amyloidosis most frequently is accompanied by isolated autonomic insufficiency, but patients with Guillain-Barré and paraneoplastic (Eaton-Lambert) syndromes, porphyria, and occasionally alcoholism may present initially with autonomic neuropathy.

TABLE 2.—*Causes of Peripheral Neuropathy That May Result in Orthostatic Hypotension*

Diabetes mellitus	Renal failure
Alcoholism	Recurrent peripheral neuropathy
Nutritional deficiency: vitamin B_{12}, folate	Amyloidosis
Guillain-Barré syndrome	Porphyria
Toxins, drugs	Infectious agents: diphtheria, tetanus, botulism
Heavy metals	Systemic collagen vascular diseases
Hereditary	Syringomyelia
Hansen's disease	Tabes dorsalis
Paraneoplastic (Eaton-Lambert) syndrome	

Specific Syndromes Causing Chronic Orthostatic Hypotension

Diabetes Mellitus

Diabetes mellitus is the most common cause of autonomic neuropathy but rarely results in disabling orthostatic hypotension.[20] Autonomic neuropathy usually manifests as gastrointestinal problems of chronic diarrhea and gastroparesis, but an early loss of sinus arrhythmia and decreased sweating also occur. Orthostasis may develop many years after the onset of peripheral sensory and motor neuropathy because of a loss of postganglionic nerves. A failure of venous vasoconstriction in the lower extremities and splanchnic vascular beds, reduced basal and posture-stimulated plasma norepinephrine levels, and a reduced renin response to posture have all been demonstrated in diabetic patients and contribute to the orthostasis. Insulin therapy may further complicate orthostatic hypotension in these patients because it decreases plasma volume, causes vasodilation, and increases heart rate.

Idiopathic Orthostatic Hypotension (Bradbury-Eggleston Syndrome)

The Bradbury-Eggleston syndrome is an idiopathic degeneration of the peripheral autonomic nervous system that presents late in life and afflicts men four to five times more often than women. The onset of the disease is insidious, occurring over two to five or more years.

Impotence, sphincter disturbances, and postprandial syncope are the most common presenting symptoms of patients with this syndrome, but orthostasis and supine hypertension also are common diagnostic clues. Many patients withdraw from social contact because of embarrassing episodes of syncope or near-syncope, an inability to drive at night, intolerance to heat, and urinary incontinence. Patients may give a history of treatment of hypertension with intolerance to medications; previous episodes of urinary tract obstruction, occasionally treated with transurethral resections of the prostate; cardiac catheterizations for angina in which normal coronary arteries and excellent ejection fractions were found; treatment of allergies, transient ischemic attacks, or seizures; and many urinary tract infections. Characteristically, episodes of syncope or near-syncope are not accompanied by sweating, nausea, pallor, shortness of breath, or tachycardia.[6,21,22]

Although the cause of the loss of preganglionic and postganglionic autonomic neurons is not known, the consequences of this loss are well documented. Plasma levels of norepinephrine are reduced, usually below 0.59 nmol per liter (100 pg per ml), as are urinary levels of all three catecholamines. There is a loss of cell bodies in the intermediolateral column of the spinal cord and a loss of catecholamine fluorescence in sympathetic ganglia and target organs. A substantially reduced or absent catecholamine response is seen to an upright posture and insulin-induced hypoglycemia, and there is virtually no rise in renin, angiotensin II, or aldosterone levels with an upright posture. These patients are extremely sensitive to α- and β-adrenergic agonists,[23,24] and strokes have occurred after normal doses of over-the-counter cold preparations. No cognitive dysfunction or central neurologic deficits are associated with the Bradbury-Eggleston syndrome, and most patients have a life expectancy of more than ten years, despite their advanced age at diagnosis.

Shy-Drager Syndrome (Multiple System Atrophy)

This disorder usually presents in mid- to late life as orthostatic hypotension associated with major neurologic deficits referable to the corticobulbar, corticospinal, extrapyramidal, and cerebellar systems. Lower motor neuron lesions are occasionally present as well. No sensory or cognitive impairments are present, and the peripheral autonomic nervous system appears to be intact but disconnected from the central nervous system. Cell bodies are present in the intermediolateral column of the spinal cord and in the sympathetic ganglia, and peripheral sympathetic nerve catecholamine

content and fluorescence are normal. Plasma and urine catecholamine concentrations are in the normal range and are releasable by indirect-acting sympathomimetic drugs, but do not change with an upright posture.[5]

Patients with the Shy-Drager syndrome exhibit slowly progressive deterioration, with increasing neurologic deficits, periodic respirations, difficulty swallowing, and laryngeal stridor as ominous signs. Respiratory arrest and pulmonary embolus are frequent causes of death, occurring an average of seven to eight years after the first manifestations of disease. Occasionally orthostatic hypotension will precede the onset of focal central neurologic deficits and prompt an initial misdiagnosis of the Bradbury-Eggleston syndrome.

Riley-Day Syndrome (Familial Dysautonomia)

The Riley-Day syndrome is an autosomal recessive neuropathy that affects about 1 in 5,000 Ashkenazi Jews. It is usually identified at birth or shortly thereafter by the presence of widespread neurologic deficits, including areflexia or hyporeflexia, poor motor coordination, mental retardation, a relative indifference to pain, emotional lability, and orthostatic hypotension.[9] The patient's body temperature varies widely, there is increased sweating and decreased tearing, and pulmonary infections are frequent. Infant mortality for patients with this disorder is high, but enough patients survive to adulthood to yield an average life expectancy of 22 years.

Baroreceptor Dysfunction

Baroreceptor dysfunction usually occurs late in life and is often associated with neck irradiation, trauma, surgery, or a local spread of oropharyngeal carcinoma. It is manifested by wide variations in blood pressure that are dependent on the heart rate.[23] Many patients with baroreceptor dysfunction have periods of supine and upright hypertension and receive antihypertensive medications with uniformly adverse consequences. Similarly, administering sedatives may result in dramatic falls in blood pressure. Glossopharyngeal neuralgia is a paroxysmal form of this disorder, presenting as pain in the side of the neck or jaw followed within a minute by sympathetic withdrawal and parasympathetic activation. This results in hypotension and bradycardia, which may be fatal.[17] Glossopharyngeal neuralgia is usually caused by irritative lesions of the carotid sinus nerve, but occasionally no inciting cause has been found. The successful treatment of cancer-associated baroreceptor dysfunction has usually involved the intracranial section of the caudal rootlets of the ninth and the rostral rootlets of the tenth cranial nerves.[25,26] Chronic baroreceptor dysfunction has been managed with a combination of cardiac pacemakers plus β-adrenergic blocking agents.

Dopamine-β-Hydroxylase Deficiency

Eight patients have been found to have a deficiency in dopamine-β-hydroxylase, resulting in severe orthostatic hypotension. In retrospect the disease is manifested shortly after birth, but frequently it is misdiagnosed as seizures, sudden infant death syndrome, hypoglycemia, and hypothermia. Mothers of these infants have a high incidence of spontaneous abortions and stillbirths. Cognitive function in these patients is normal. The most common clinical features of the six patients diagnosed by us are shown in Table 3.[27]

Plasma, urinary, and spinal fluid concentrations of norepinephrine and epinephrine are below detectable limits in patients with this condition, and plasma dopamine levels are greatly increased. All sympathetically mediated cardiovascular reflexes are greatly diminished, but sinus arrhythmia, increased heart rate after the administration of atropine (a parasympathetic test), and sweating (a sign of sympathetic cholinergic function) are intact. An upright posture and the administration of indirect-acting sympathetic drugs result in a doubling or tripling of plasma dopamine levels, and inhibiting dopamine synthesis raises the blood pressure. These data are consistent with the conclusion that sympathetic nerves release dopamine instead of norepinephrine in this disorder.

TABLE 3.—*Manifestations of Dopamine-β-Hydroxylase Deficiency (n=6)*

Symptom	*Frequency, %*
Severe orthostatic hypotension	100
Retrograde ejaculation	100
Ptosis	67
Complicated perinatal course	67
Nocturia	67
Hyperextensible joints	50
Nasal stuffiness	50

Evaluation of Orthostatic Hypotension

Patients with any form of orthostatic hypotension usually present with similar symptoms. On assuming an upright posture they may experience lightheadedness, dizziness, syncope, swaying, focal cerebral ischemia manifested by receptive or expressive aphasia or seizures (usually clonic jerks), angina pectoris, headache referred to the back of the head or neck, or tunnel vision. Symptoms and the likelihood of syncope are increased after meals, in hot environments such as after showers, and after consuming alcohol. With syncope, patients typically awaken almost immediately after assuming a horizontal position, without drowsiness or postictal confusion. Additional complaints may include a parkinsonian syndrome, diffuse neurologic defects, recurrent urinary tract infections, intolerance to antihypertensive agents, sleep apnea, and hoarseness.

Physicians must first consider nonautonomic causes and reverse correctable factors causing orthostasis. About 50% of our consultations for orthostatic hypotension involve drugs, with antihypertensive or diuretic agents, tricyclic antidepressants, vasodilators, alcohol, nitrates, narcotics, major and minor tranquilizers, marijuana, nasal sprays, and diet pills the most common offenders.[21] Severe volume depletion should be obvious from the clinical setting and history; subacute volume contraction from pheochromocytoma, renovascular hypertension, Addison's disease, and overenthusiastic dialysis or diuresis should be considered. Tachyarrhythmias, bradyarrhythmias, and heart block should be apparent from the circumstances surrounding the syncope, and flushing due to carcinoid, pheochromocytoma, and mastocytosis may be present. If the history clearly indicates that symptoms occur while the patient is supine, orthostatic hypotension may be excluded as a cause. The presence of mitral valve prolapse, pregnancy, large venous varicosities, fever, gastrectomy, sympathectomy, and prolonged recumbency or weightlessness may also be revealed by the history. In the absence of

these conditions, the patient will usually have a primary or secondary form of autonomic failure, and the physician should obtain a history, signs, and symptoms of peripheral neuropathy. The nonautonomic causes of orthostasis typically present abruptly, in less than a month, whereas orthostatic hypotension occurring as a result of autonomic failure usually has progressed over a period of two to five years.

The physical examination of a patient in autonomic failure will show a fall in blood pressure of at least 25 mm of mercury systolic and 10 mm of mercury diastolic within a minute of assuming an upright posture, with an increase in heart rate usually less than 5 bpm and always less than 10 bpm. This change in blood pressure is coincident with the onset of symptoms and is reproducible. Virtually all other causes of orthostatic hypotension will result in a moderate to pronounced rise in heart rate when blood pressure falls. More than 50% of patients with autonomic failure have supine hypertension. The eye examination may reveal unequal or irregular pupils that may be strikingly miotic and unable to dilate with pain. The skin is pale and dry with anhidrosis, and evidence of weight loss is often present. Sphincter tone is usually decreased. Tremor, dysdiadochokinesia, rigidity, and paucity of movement may be present, with or without focal neurologic signs.

Autonomic Function Testing

Many tests of autonomic function are available (Table 4). During the physical examination, the patient's supine, seated, and standing (30 to 60 seconds after assuming the upright position) blood pressures should be noted. The length of time the patient can stand without symptoms of cerebral hypoperfusion occurring has important diagnostic and prognostic implications. Standing times in excess of 10 minutes indicate insignificant orthostatic hypotension, whereas patients whose symptoms occur in less than 60 seconds can rarely live at home without assistance. Variations in heart rate can be estimated during the examination by observing a sinus arrhythmia during respirations, heart rate increases and decreases during and after the Valsalva maneuver, and heart rate slowing with carotid massage. Hyperventilation for more than 30 seconds will reduce systolic blood pressure in patients with autonomic failure by more than 20 mm of mercury, with a decrease of less than 10 mm of mercury being normal.[28] Repeated blood pressure measurements after a meal will often show the systolic pressure to be reduced by 20 to 60 mm of mercury in patients with autonomic failure.

Formal autonomic function testing may differentiate the various forms of autonomic dysfunction by indicating the presence or absence of appropriate blood pressure and heart rate changes with deep breathing and to the Valsalva maneuver, an increase in blood pressure during isometric exercise (handgrip test) and in response to pain (cold pressor test), the presence of sweating, increased blood pressure during arithmetic computations, and supersensitivity to α- and β-adrenergic agonists. Such testing may also assess the function of the baroreceptor reflex response to increases and decreases in blood pressure and detect the absence of a parasympathetic nervous system (if atropine fails to increase the heart rate), the absence of the sympathetic nervous system (if tyramine infusion fails to increase blood pressure or elevate plasma catecholamine levels), and the presence of baroreceptor dysfunction (if the blood pressure varies only with the heart rate). Syncope produced by a passive upright posture on a tilt table may occur in patients with increased sensitivity of cardiac mechanoreceptors, who otherwise may have normal autonomic function.

Laboratory evaluations in addition to standard admission tests should include obtaining specimens with the patient supine and standing to measure plasma concentrations of norepinephrine, epinephrine, and dopamine, 24-hour urine catecholamine and metabolite levels, a urine porphyrin screen, blood gas determinations, a Holter monitor, and, in the presence of neurologic deficits, a computed tomographic scan or magnetic resonance imaging scan of the head. If deficits in cardiovascular reflexes are present, many patients also have a neurogenic bladder, and a postvoiding residual evaluation and a cystometrogram are warranted. If a peripheral neuropathy is suspected, tests appropriate to the disorders listed in Table 2 should be done, with emphasis on obtaining a rectal or gingival biopsy for the diagnosis of amyloidosis.

TABLE 4.—*Tests of Autonomic Function*

Test	*Normal Response*
Standing time	>10 min
Orthostatic blood pressure (BP)	Systolic BP falls <10 mm of mercury, diastolic BP rises or remains steady
Sinus arrhythmia/respiratory variation	Longest to shortest RR interval >1.2
Valsalva maneuver	Baseline to shortest RR >1.4
Carotid massage	Heart rate (HR) slowing >10 bpm
Hyperventilation	BP decrease <10 mm of mercury
Handgrip test/isometric exercise	BP increase >10 mm of mercury
Cold pressor test	BP increase >10 mm of mercury
Mental arithmetic	BP increase >5 mm of mercury
Postprandial BP monitoring	BP decrease <10 mm of mercury
Sweat test	Diffuse sweating
Orthostatic catecholamine levels	≥ Twofold increase on standing
Drug responses	
Atropine	Increased HR > 25 bpm
Phenylephrine	BP_{25} = 200 μg, HR decrease
Isoproterenol	HR_{25}, BP_{-25} = 5 μg
Tyramine	BP_{25} = 2 mg, increased norepinephrine level
Epinephrine eye drops	No change in pupil size

BP_{25} = 25 mm of mercury BP increase, BP_{-25} = 25 mm of mercury BP fall, HR_{25} = 25 bpm HR increase

Management of Chronic Orthostatic Hypotension

The goals of managing chronic orthostatic hypotension are to obtain adequate cerebral perfusion with the patient in the upright position, to avoid situations that promote orthostasis, and to minimize symptoms and side effects of therapy. Achieving these goals will mobilize bedridden or housebound patients, maximize their functional capacity, and improve their quality of life.[22,29]

Physical Measures

Patients with autonomic failure have inadequate renal sympathetic function and renin-angiotensin-aldosterone activity to retain sodium and maintain an adequate blood volume. Increased salt intake, particularly early in the day, to more than 150 mEq per day is helpful in balancing the large volume losses that accompany patients' profound nocturia. The nocturia may be reduced substantially by elevating the head of the bed 15 to 20 cm (6 to 8 in) with shock blocks. This will reduce many patients' supine hypertension and thereby minimize the pressure natriuresis they experience. Even in patients without supine hypertension, elevating the head of the bed will promote fluid retention and lessen the orthostasis. Rest during the daytime should likewise be in the reverse Trendelenburg position in bed or in a reclining chair. Patients should be cautioned to rise from the lying position in stages, particularly in the morning. Supine hypertension may also be avoided by drinking alcohol or consuming a small meal at bedtime.

TABLE 5.—*Situations to Avoid in Chronic Orthostatic Hypotension*

Large meals	Coughing spells
Prolonged recumbency	Hot weather
Isometric exercise	Rapid ascent to high altitude
Standing motionless	Hot baths or showers
Alcohol	Fever
Working with arms above shoulder level	Hyperventilation
Straining at stool or with voiding	

The central blood volume may be increased by physical measures as well. Wearing heavy support stockings or pantyhose (Jobst), with or without an abdominal binder, while upright will reduce the 400- to 700-ml fall in central blood volume caused by standing. Pressure garments should be removed before reclining to avoid supine hypertension and diuresis. Antigravity or antishock suits have also been advocated, but their practical usefulness is limited. Presyncopal symptoms while standing should be treated promptly by having the patient squat, use a small portable stool, assume a stooped posture, tighten the leg muscles, or sit down with the feet elevated. Low levels of exercise may be tolerated well as long as the temperature is cool. The ideal form of exercise is swimming because hydrostatic forces perfectly oppose the reduction in central blood volume caused by gravity.

Patient education is a key ingredient of the successful management of orthostatic hypotension, both for situations to avoid and for the means of handling low blood pressure. Table 5 lists various situations that should be avoided or modified to prevent orthostasis or syncope. In addition, alcohol use and ingesting large meals may produce substantial falls in blood pressure, so avoiding ethanol consumption and taking several small meals during the day may alleviate recurrent episodes of orthostasis. A rapid ascent to high altitude may provoke hyperventilation and exacerbate orthostasis.

The enhanced sensitivity of these patients to sympathomimetic amines has resulted in malignant hypertension and strokes after the ingestion of normal doses of over-the-counter cold preparations. Likewise, diet pills, nasal sprays, and eye drops should be used with caution, if at all. Vasodilators, β-agonists, and diuretic drugs also should be avoided. These patients are also at higher risk of adverse reactions to anesthesia, for many reasons: Positive pressure respiration impairs the return of blood to the heart and lowers the blood pressure, many anesthetic agents produce vasodilation, the respiratory drive may be abnormal, supersensitivity to vasoconstrictor agents may result in anesthetic catastrophes, the absence of vagal tone may alter the response to atropine, abnormal sweating and pupillary responses may impair adequate monitoring, and the adrenal gland may not react appropriately to surgical stress. For these reasons, we recommend preanesthetic placement of a Swan-Ganz catheter for monitoring cardiac filling pressures and close intraoperative and postoperative management of the patient until full consciousness is regained.[30]

Drug Therapy

The goals of drug therapy are to increase the circulating blood volume and to support the patient through periods of the day or situations likely to produce orthostasis. Table 6 shows the agents used for these purposes.

Fludrocortisone may be used to increase the blood volume and enhance the pressor sensitivity to vasoconstrictor agents. Doses of 0.1 mg once or twice a day, slowly increased to a total of 1 mg per day, may be helpful, but pedal edema, hypokalemia, and supine hypertension may limit the dose of this agent, and some degree of tachyphylaxis will develop. Patients with autonomic dysfunction are supersensitive to α- and β-adrenergic agonists, and these agents must be used at low doses with careful monitoring of blood pressure.[23,24] Pressor agents such as phenylpropanolamine, phenylephrine, ephedrine, yohimbine hydrochloride, and ergotamine tartrate will raise blood pressure for one to four hours, and a properly instructed patient may use these during the day. We have observed a desensitization in response to the direct-acting sympathomimetics, which may be restored after a drug holiday of a week to ten days. Yohimbine is of value

TABLE 6.—*Drug Therapy in Chronic Orthostatic Hypotension*

Volume-increasing agents	Preventers of postprandial hypotension
Fludrocortisone acetate	Caffeine
Vasopressin	Indomethacin
Sympathomimetics	Somatostatin
Phenylpropanolamine	Dopamine receptor antagonists
Phenylephrine	Domperidone
Ephedrine hydrochloride	Metoclopramide hydrochloride
Midodrine	Miscellaneous drugs
Amphetamines	Nonselective β-blockers
Ergotamine tartrate	Nighttime vasodilators
Yohimbine hydrochloride	
Clonidine hydrochloride	
Dihydroxyphenylserine	

in patients with the Shy-Drager syndrome and in patients less severely affected by the Bradbury-Eggleston syndrome because the drug potentiates the release of catecholamines from sympathetic nerve terminals. It is also of particular value in diabetic autonomic neuropathy because of its blood pressure-raising actions and its potentiation of insulin release.

Both indomethacin and caffeine have mild blood pressure-raising effects and may reduce postprandial hypotension approximately 50% by limiting the increase in splanchnic blood flow after meals. We routinely advise our patients to drink the equivalent of two cups of caffeinated coffee when eating a large meal. Clonidine may also exert dramatic pressor responses in these patients because of its peripheral α_2-adrenergic agonist actions, but dry mouth and sedation have limited the number of patients who may be successfully managed with this agent.[31] Somatostatin and its analogues raise the blood pressure somewhat and antagonize postprandial hypotension but require intradermal injection.

Nasal insufflation of vasopressin has also been advocated both for its volume-retaining and its vasoconstrictor actions, but with prolonged use patients are prone to the development of electrolyte disorders. Nonselective β-blockers are often useful in milder cases because the β_2-antagonism prevents vasodilation in muscle vascular beds, thereby limiting the fall in blood pressure with an upright posture and exercise.

Nighttime supine hypertension can be reduced by a bedtime snack, a glass of wine, or short-acting vasodilators such as hydralazine hydrochloride or small doses of nifedipine. Vasodilators should be used with caution, however, because patients will usually continue to experience nocturia. Antihistamines have little effect on blood pressure in patients with autonomic failure but are the mainstay of therapy in patients with systemic mastocytosis. Levodopa often aggravates orthostasis in patients with parkinsonian symptoms, and occasionally the use of a combination of levodopa and carbidopa reduces the extent of drug-induced orthostasis. Investigational approaches to therapy in patients with autonomic failure have included posture-activated norepinephrine pumps and atrial tachypacing, but these appear to offer little practical benefit. Atrial tachypacing combined with β-blockade may alleviate much of the disability in patients with baroreceptor dysfunction.

A few patients with orthostatic hypotension have elevated plasma dopamine levels and may benefit from dopamine antagonists, such as metoclopramide hydrochloride or domperidone, or from the inhibition of dopamine synthesis by metyrosine.[1] The defect in norepinephrine synthesis present in patients with dopamine-β-hydroxylase deficiency may be circumvented by treatment with dihydroxyphenylserine, which is decarboxylated within sympathetic neurons directly to norepinephrine.[1]

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